Practice advisory update: Antiseizure medication withdrawal in seizure-free patients

Report of the Guideline Subcommittee of the American Academy of Neurology

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Approved by the Guideline Development, Dissemination, and Implementation Subcommittee on October 20, 2018; by the AAN Quality Committee on May 24, 2021; and by the AAN Institute Board of Directors on October 13, 2021.

This guideline was endorsed by the Child Neurology Society on November 1, 2021.

STUDY FUNDING

This practice guideline was developed with financial support from the AAN. Authors who serve or have served as AAN subcommittee members or as methodologists (D.G., A.P., J.A.F., B.T. and C.H.) were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed. All authors on the panel were reimbursed by the AAN for expenses related to travel to in-person meetings.

DISCLOSURE

D. Gloss reports no relevant disclosures.

K. Pargeon reports no relevant disclosures.

A. Pack served on the editorial board of the journal Epilepsy Currents; receives royalties from UpToDate; receives funding from the NIH for serving as coinvestigator and site principle investigator for the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study; received funding from Bayer for serving as a co-investigator on a study on women with epilepsy initiating a progestin IUD; and her husband serves as the CMO for Regenxbio, for which he receives salary and stock options.

J. Varma reports no relevant disclosures.

J. French receives NYU salary support from the Epilepsy Foundation and for consulting work and/or attending Scientific Advisory Boards on behalf of the Epilepsy Study Consortium for

Adamas, Aeonian/Aeovian, Anavex, Arkin Holdings, Arvelle Therapeutics, Inc., Athenen Therapeutics/Carnot Pharma, Baergic Bio, Biogen, BioXcel Therapeutics, Cavion, Cerebral Therapeutics, Cerevel, Crossject, CuroNZ, Eisai, Eliem Therapeutics, Encoded Therapeutics, Engage Therapeutics, Engrail, Epiminder, Equilibre BioPharmaceuticals, Fortress Biotech, Greenwich Biosciences, GW Pharma, Janssen Pharmaceutica, Knopp Biosciences, Lundbeck, Marinus, Mend Neuroscience, Merck, NeuCyte, Inc., Neurocrine, Otsuka Pharmaceutical Development, Ovid Therapeutics Inc., Passage Bio, Praxis, Redpin, Sage, SK Life Sciences, Sofinnova, Stoke, Supernus, Synergia Medical, Takeda, UCB Inc., West Therapeutic Development, Xenon, Xeris, Zogenix, Zynerba; has received research support from the Epilepsy Research Foundation, Epilepsy Study Consortium (Funded by Andrews Foundation, Eisai, Engage, Lundbeck, Pfizer, SK Life Science, Sunovion, UCB, Vogelstein Foundation) Epilepsy Study Consortium/Epilepsy Foundation (Funded by UCB, Engage, Neurelis, SK Life Science), GW/One8 Foundation/FACES and NINDS; is on the editorial board of Lancet Neurology and Neurology Today; is Chief Medical/Innovation Officer for the Epilepsy Foundation for which NYU receives salary support; and has received travel reimbursement related to research, advisory meetings, or presentation of results at scientific meetings from the Epilepsy Study Consortium, the Epilepsy Foundation, Arvelle Therapeutics, Inc., Biogen, Cerevel, Engage, Lundbeck, NeuCyte, Inc., Otsuka, Sage, UCB, Xenon, Zogenix.

B. Tolchin has received research funding from the Department of Veterans Affairs, the C.G. Swebilius Trust, and the American Academy of Neurology and has received honoraria from Columbia University Medical Center and the International League Against Epilepsy.

D. Dlugos receives travel reimbursement for protocol development conferences and clinical trial investigator meetings from Marinus, Ovid/Takeda, Ultragenyx, Pfizer, Biogen, BioMarin, and Xenon; receives research funding for serving as site investigator on clinical trial research grants awarded to CHOP from Zogenix, Greenwich Biosciences, Brain Sentinel, Neurelis, Q-State, Aquestive, Bio-Pharm, SK Life Sciences, and Encoded Therapeutics; has received honoraria and/or travel support for CME and other educational programs from Wake Forest University School of Medicine, American Epilepsy Society, American Academy of Neurology, Epilepsy Foundation of America, Epilepsy Foundation of North Carolina, Medscape, Miller Medical Communications, Ecuador Neurology Project, Ministry of Health of the United Arab Emirates, Seoul National University, and the Chinese Pediatric Society; performs EEGs as 20% of clinical effort (clinical effort is only 25% of work); and receives salary support from NIH, Commonwealth of Pennsylvania Department of Health, Pediatric Epilepsy Research Foundation, and The Epilepsy Study Consortium.

M. Mikati holds pending patent for gene therapy of ATPase related diseases, including hemiplegia of childhood; serves on editorial boards of the following journals: *Annals of Neurology*, *Epileptic Disorders,* and *Epilepsy Research*; has received travel reimbursement from AHRQ for travel to Cure AHC conferences; receives royalties (about $50 per year) from Springer for a developmental pediatrics textbook; spends an estimated 20% of clinical effort ordering and reading EEGs; has received research support from NIH for a study on which he serves as a consultant, NIH 2036303 (2014-2022): Undiagnosed Diseases Network Clinical Site, an integrated and diverse genomic medicine program for undiagnosed diseases, a study to detect

genetic etiologies in patients with disorders of undiagnosed conditions; and has reviewed a medico-legal case regarding an intracranial bleed in an infant.

C. Harden receives royalties from UpToDate and Wiley; serves on the speakers' bureau for UBC; has received research support from NINDS of the National Institutes of Health (NIH) and the Epilepsy Therapy Project. In September 2018, Dr. Harden accepted a new employment position with Xenon Pharmaceuticals and recused herself from further participation on the panel. Prior to accepting the employment position, Dr. Harden contributed to the development of this guideline, therefore she is listed as an author. After she was recused, the panel continued the development process with internal review of the manuscript, an updated search, a vote on the recommendations, and peer-review.

GLOSSARY

ASM: antiseizure medication

AAN: American Academy of Neurology

CI: confidence interval

COI: conflict of interest

CPG: clinical practice guideline

CV: curriculum vitae

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation

GS: Guideline Subcommittee

GTCS: generalized tonic-clonic seizure

HR: hazard ratio

MRC: Medical Research Council

OR: odds ratio

RR: relative risk

ABSTRACT

Objective: To update a 1996 American Academy of Neurology practice parameter.

Methods: The authors systematically reviewed literature published January 1991 to March 2020.

Results: The long-term (24–60 months) risk of seizure recurrence is possibly higher among adults who have been seizure-free for 2 years and taper antiseizure medications (ASMs) vs those who do not taper ASMs (15% vs 7% per the 1 Class I paper addressing this issue). In pediatric patients, there is probably no significant difference in seizure recurrence between those who begin tapering ASMs after 2 years vs 4 years of seizure freedom, and there is insufficient evidence of significant difference in risk of seizure recurrence between those who taper ASMs after 18 months of seizure freedom and those tapering after 24 months. There is insufficient evidence that the rate of seizure recurrence with ASM withdrawal following epilepsy surgery after 1 year of seizure freedom vs after 4 years is not significantly different than maintaining patients on ASMs. An epileptiform EEG in pediatric patients increases risk of seizure recurrence. ASM withdrawal possibly does not increase the risk of status epilepticus in adults. In seizure-free adults, ASM weaning possibly does not change quality of life. Withdrawal of ASMs at 25% every 10 days to 2 weeks is probably not significantly different than withdrawal at 25% every 2 months, in children who are seizure-free, in more than 4 years of follow-up.

Recommendations:

Fourteen recommendations were developed.

INTRODUCTION

Epilepsy is a common disease of the brain and accounts for approximately 1% of the global burden of all disease.[1,2] In the United States alone, an estimated 70,000–200,000 adults per year will present with a first unprovoked seizure.[3,4] The purpose of prescribing an antiseizure medication (ASM) is to render patients with epilepsy seizure-free, a task that is accomplished approximately two-thirds of the time.[5,6] When seizure freedom is achieved, there is the inevitable question of if and when ASMs should be weaned. Currently, epilepsy is not considered resolved until a patient is seizure-free for at least 10 years and off ASMs for at least the last 5 years.[7]

This practice advisory updates the 1996 American Academy of Neurology (AAN) practice parameter on the same topic,[8] which recommended that after assessing the risks and benefits for both patient and society of a recurrent seizure, the discontinuation of ASMs may be considered if the patient meets the following profile:

- Seizure-free 2–5 years while taking ASMs (mean 3.5 years)
- Single type of partial seizure (simple partial or complex partial or secondary generalized tonic-clonic seizure [GTCS]) or single type of primary generalized seizures
- Normal neurologic examination results/normal IQ
- EEG normalized while taking ASMs

A Cochrane review addressed this question in children without generalized seizures but was unable to address this issue in adults or in children with generalized seizures.[9] This review recommended treatment until the child was seizure-free for at least 2 years before considering withdrawing ASMs, particularly if there were focal (i.e., partial) seizures or EEG abnormalities (presumably any but it is left unspecified in the review).

The panel for this practice advisory examined questions similar to those addressed in the Cochrane review but allowed broader inclusion criteria and used the AAN methodology to craft recommendations. The aim of the practice advisory is to provide information that will inform the care of epilepsy patients.

For patients with epilepsy taking ASMs who have been seizure-free for at least 12 months, does stopping ASMs, compared with not stopping:

1. increase the risk of seizure recurrence, and are there risk factors for seizure recurrence?
2. increase the risk of status epilepticus?
3. reduce medication-related side effects
4. change quality of life?
5. change the risk of mortality?
6. change any of the above risks based on the speed of ASM withdrawal?

Data for children were analyzed separately from data for adults because of biological differences in risk of seizure recurrence between the two groups. We defined adults as those aged 18 years or older and children as those younger than 18 years. We also distinguished focal (i.e., partial) from generalized seizures because of differences in the underlying mechanism causing epilepsy.

DESCRIPTION OF THE ANALYTIC PROCESS

In 2012, the Guideline Subcommittee (GS) of the AAN (Appendix 1 and Appendix 2) convened a panel of clinicians with expertise in epilepsy. The panel included content experts (D.G., K.P., J.V., J. A.F., C.H.), a methodology expert (D.G.), AAN GS members (J.A.F., C.H.). In 2020, the

GS member B.T. was added to the panel, and 2 content experts with expertise in pediatric neurology, D.D. and M.M, were added to the panel. Per criteria for AAN Practice Advisories, appointing patient advocates/representatives to the panel was optional, and none were appointed.

Each potential author was required to submit an online COI form and a copy of his or her curriculum vitae (CV). The panel leadership, consisting of the lead developer (D.G.), the AAN methodologist (D.G.), and AAN staff persons (E.L., T.G., S.M.), reviewed the COI forms and CVs for financial and intellectual COI. These documents were specifically screened to exclude those individuals with a clear financial conflict and those whose profession and intellectual bias would diminish the credibility of the review in the eyes of the intended users. As required by AAN policy, the lead developer (D.G.) had no COIs as defined at project initiation. At project initiation and until September 2018, one of the five practice advisory developers (J.A.F.) was determined to have relevant COIs, which were judged to be not significant enough to preclude this developer from authorship. One of the content experts added to the panel in 2020 (D.D.) also was determined to have relevant COIs judged to be not significant enough to preclude participation. Both of these judgments were made with the leadership team of the AAN GS. Although one of the developers (C.H.) had no conflicts of interest (COI) at the time the project was initiated, she accepted a new employment position with Xenon Pharmaceuticals in September 2018. Because of this conflict, she recused herself from further participation on the panel at that time as required by the AAN clinical practice guideline development process manual.[10] A member of the GS with content expertise (A.P.), and no conflicts of interest, was appointed to the panel in October of 2018 to replace C.H. Prior to accepting the employment position, C.H. contributed to the development of this guideline, therefore she is listed as an

author. After she was recused, the panel continued the development process with internal review of the manuscript, an updated search, a vote on the recommendations, and peer-review.

Outcome criteria

We addressed the following outcome measures, measured at 12 months or more, comparing those who withdrew from and those continuing taking ASMs:

1. seizure relapse. These data were divided between children and adults and between those with electroclinical syndromes and epilepsy surgery.
2. risk factors for either higher or lower rates of seizure recurrence that give odds ratios (ORs) at the same time points as measured by the chance of seizure freedom
3. quality of life data available at the same time points
4. occurrence of status epilepticus
5. mortality

Variables

We did not prespecify the variables to be considered; instead, we accepted anything the included papers found. We hoped it would be more likely to produce meaningful evidence without prespecified limitations. For any question with 10 or more trials, a funnel plot was preplanned to estimate publication bias.

There was one post-hoc decision imposed by GS after a review of the initial manuscript, in which patient-reported GTCS confirmed by a clinical coordinator would be enough to qualify for

Class III, as this would be considered adequate for a reliable patient-reported outcome. All full-text articles were re-reviewed for inclusion due to this post-hoc decision.

In April 2013, Medline, CINAHL, DARE, CENTRAL databases were searched (Appendix 3), for articles published between January 1991 and April 2013 for relevant peer-reviewed articles that met inclusion criteria, published in English. This search yielded 2,148 articles. The panelists reviewed the article titles and abstracts for potential relevance. In addition, the 17 articles included in the original 1996 AAN practice parameter and articles reviewed by the Cochrane review on this topic[9] were reviewed for inclusion. Of the reviewed abstracts, 154 were identified as potentially relevant and their corresponding articles obtained for full-text review. Each of the 154 articles was reviewed by 2 panel members working independently of each other. Disagreements in article ratings were resolved by discussion. During full text review, there was evidence for an additional question regarding the speed of withdrawal; thus, it was added to the list of questions, and abstracts were re-reviewed to ensure that papers relevant to this question were included. No additional papers were included. The panelists selected 13 articles for inclusion in the analysis. An updated literature search completed in December 2016 identified an additional 106 potentially relevant articles, none of which were included.

A third literature search was completed in March 2020 to identify articles published since December 2016. Ten additional articles were identified for full text review, but no additional studies were included in this review, as they either did not answer the questions of the guideline or were classified as Class IV.

When articles appeared to include subsets of patients who were incorporated in previous publications, all known information (so long as the paper was rated above Class IV) was

included to provide the most comprehensive information possible. This resulted in the addition of two papers. When assigning confidence in evidence, studies with multiple papers examining the same or parts of the same cohorts were counted once.

Selected articles contained information relevant to the 6 questions posed above and had acceptable study designs, including randomized and nonrandomized studies and prospective and retrospective case series published after 1991 that had a control group. We chose to examine studies after 1991 because the 1996 practice parameter did not contain literature beyond this point. Reviews, editorials, and meta-analyses were excluded. Studies of 29 or fewer participants were excluded because any confidence intervals formulated from such small studies would not be informative. Also excluded were studies that included less than 20 percent or an unknown number of patients who have had a single seizure, rather than epilepsy, studies that would be rated as Class IV, studies not relevant to the clinical questions, studies including participants who had unrelated diseases or were outside of the study population, and articles that were not peer reviewed. Each of the 164 articles was rated by 2 panel members using the AAN criteria for classification of prognostic and treatment[10] (Appendix 4), with the following five explicit clarifications determined by the panel a priori:

1. Any articles that addressed specific electroclinical syndromes were considered separately, as electroclinical syndromes have a known time-course.
2. Articles addressing epilepsy surgery patients were considered separately as they have substantially different characteristics and histories than typical seizure patients.
3. Unblinded cohort studies could be rated Class II, provided they were shown to have a careful matching of possible confounding covariates and met the other characteristics for Class II. This decision was made because there were amendments to the current process

in progress that would allow unblinded cohorts to be Class II under specific narrow circumstances.

4. For open-label cohort studies, the use of seizure diaries, or an explicit statement that patients determined outcomes would be enough to qualify the study as Class III if other characteristics for Class III were fulfilled (as was done in the vagus nerve stimulation update[11]). This decision was based on the fact that seizure recurrence is not necessarily objective (such as auras without motor component); however, seizure diaries represent an outcome determined independently from the investigators.
5. Because of the broad range of physician and patient preference, the author panel decided that if there was only very low confidence in evidence in non-counseling recommendations, the articles would not go through a modified form of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)/modified Delphi process and the question would be given a 'U' recommendation for insufficient evidence; otherwise, panel authors would be creating a consensus-only recommendation.

A modified GRADE process (Appendix 5) was used to develop conclusions. In this process, the evidence is analyzed on the basis of various parameters of risk of bias (multiple types), consistency, directness, precision, and publication bias and upgraded or downgraded according to the AAN process[10].

The panel followed the AAN process[10] to formulate a rationale for each of the recommendations. The rationales precede the recommendation statements. According to the AAN process, 4 types of premises can be used to support recommendations: (1) evidence-based conclusions from the

systematic review, (2) generally accepted principles of care, (3) strong evidence from related conditions, and (4) deductive inferences from other premises. Recommendations must always be supported by at least one premise (Appendix 6). The level of obligation of the recommendations was assigned using a modified Delphi process that considered the following prespecified domains: the confidence in the evidence systematically reviewed, the acceptability of axiomatic principles of care, the strength of indirect evidence, and the relative magnitude of benefit to harm. Additional factors explicitly considered by the panel that could modify the level of obligation include judgments regarding the importance of outcomes, cost of compliance with the recommendation in relation to benefit, the availability of the intervention, and anticipated variations in patients' preferences. The level of obligation was indicated using standard modal operators ("must," "should,", or "may"). "Must" corresponds to Level A, very strong recommendations; "should" to Level B, strong recommendations; and "may" to Level C, weak recommendations.[10]

ANALYSIS OF EVIDENCE

For patients with epilepsy taking ASMs who have been seizure-free for at least 12 months, does stopping ASMs compared with not stopping increase the risk of seizure recurrence, and are there risk factors for seizure recurrence?

Adults

One Class I study[12] and 3 Class III studies[13-15] examined this question. The Class I study[12] enrolled 160 adults who had been seizure-free for 2 years. Patients were randomized to ASM withdrawal, using placebo, or ASM continuance. The risk of recurrence during the 12 months of

the study was not significantly different between the groups: 15% of the withdrawal group vs 7% of the nonwithdrawal group experienced seizures following ASM withdrawal (relative risk [RR] 2.46, 95% confidence interval [CI] 0.85–7.08, p=0.95). The follow-up portion of the study was Class IV. The risk of seizure recurrence is low compared with other studies with a higher risk of bias.

One Class III study was a nonrandomized, mostly adult, cohort trial in which patients and their caregivers decided whether to withdraw ASMs.[13] Study participants were patients with epilepsy who were seizure-free for at least 2 years and receiving stable ASM monotherapy. At 60 months, the chance of remaining seizure-free was 68% (95% CI 62%–74%) among patients who continued treatment and 48% (95% CI 38%–57%) among patients who did not. During the 60 months of follow-up, after multivariate adjustment, the hazard ratio (HR) for seizure recurrence in patients in whom ASMs were withdrawn was 2.9 (95% CI 1.8–4.6, p<0.001).

One Class III study randomized 1,013 patients who were seizure-free for at least 2 years to continued ASM treatment vs ASM withdrawal.[14] The study was included because a majority of seizure recurrences were GTCSs (74%) and, thus, considered objective. The study primarily included adults (median age was 26–27 years and medians were presented by group; however, 25% of patients were aged 16–17 years at enrollment). Data were not presented separately between adults and children; therefore, the study was used to inform the adult question. The baseline groups were not equivalent. For example, those with a history of attempted ASM withdrawal (OR 0.6, 95% 0.5–0.8, p<0.0001) as well as those with a driving license were less likely to be randomized (OR 0.13, 95% CI 0.1–0.18, p<0.0001), and those with special schooling

were more likely to be randomized (OR 5.4, 95% CI 3.5–9.4, $p<0.0001$). Of patients who withdrew ASMs, 43% (221/510) had a recurrent seizure, compared with 26% (133/503) of patients who continued taking ASMs (OR = 2.12; 95% CI 1.63–2.77, $p<0.0001$).

Another Class III study[15] compared 168 recurrences out of 221 (76%) patients in the withdrawal group, and 100 recurrences out of 133 patients (75%) in the ASM continuation group having multiple recurrences. There was not a statistically significant difference in risk of more than 1 seizure if there was a single recurrence (OR 1.04, 95% CI 0.63–1.72, $p<0.86$).

Conclusions

In adults who have been seizure-free for 2 years, there is not evidence to support or refute a difference in the rate of seizure recurrence in those who taper ASMs versus those who do not. The point estimate is 2 times greater seizure recurrence in those who taper vs those who do not (15% vs 7%), although this difference is not significantly different. The strength of evidence was downgraded due to imprecision. There were discussions about how to handle the fact that the study had lower risk of seizure recurrence than all other studies, and it was downgraded again for a lack of generalizability because the authors believed that this study represented a different population than is typical (very low confidence, one Class I study downgraded for imprecision and generalizability). In the long term (24–60 months), the risk of seizure recurrence is possibly higher among those who taper ASMs (low confidence, 2 Class III studies).

Children

Two Class II and two Class III studies addressed the risk of seizure recurrence after stopping ASMs and risk factors for recurrence in children. In one Class II study, 57 patients (mean age 9.5 years) who had seizure control for at least 2 years were tapered either at 2 years or 4 years of seizure freedom.[16] The Kaplan-Meier survival curve did not demonstrate significant differences in seizure freedom over the 54 months of follow-up. In the other Class II study, 149 patients (mean age of 11 years) who had been seizure-free for at least 18 months were randomized into tapering at 2 years or 4 years of seizure freedom.[17] Kaplan-Meier survival curves over the 300 weeks of follow-up were not significantly different between the two groups. In the Class III study, patients who had been seizure-free for 18 months were randomized to taper ASMs immediately or to wait an additional 6 months (taper at 24 months). Of those tapering at 18 months, mean age was 6.7 years. Of those tapering at 24 months, mean age was 5.8 years.[18] There was no significant difference for seizure recurrence risk during the follow-up period. During follow-up, 12 of 41 (29%) patients who tapered at 18 months had seizure recurrence during their 38 months of mean follow-up; 14 of 39 (36%) who tapered at 24 months had recurrence during their 24 months of mean follow-up, yielding an RR of 0.82 (95% CI 0.43–1.534). A second Class III study of 238 children (mean age of 8.8 years), were randomized to treatment for 1 or 3 years; both groups were followed for 5 years.[19] After correcting for multiple comparisons (Bonferroni correction), there were no significant differences in the percentage of children seizure-free during the last 6 months of observation (72% vs 84%, RR 0.857, 95% CI 0.740–0.991, $p>0.05$), or the entire follow-up period (32% vs 41%, RR 0.775, 95% CI 0.539–1.115, $p>0.05$). In this trial, 8% of children continued to have some seizures with treatment, and 2% became medication resistant, which they defined as more than one seizure per month.

Conclusions

There is probably not a significant difference in seizure recurrence in children who taper ASMs at 2 vs 4 years (time of seizure freedom) (moderate confidence in evidence, two Class II studies). There is insufficient evidence whether there is a significant difference in the risk of seizure recurrence in children who taper ASMs at 18 vs 24 months (very low confidence, one Class III study).

Electroclinical syndromes

Electroclinical syndromes have some or all of the following characteristics: specified age range of onset, specific developmental changes, specific physical characteristics, specific seizure provoking/triggering factors, and specific EEG features.[20] None of the included studies with ratings higher than Class IV addressed the question of drug withdrawal and risk of seizure recurrence in specific electroclinical syndromes.

Epilepsy surgery patients

A single Class III study addressed the question of drug withdrawal and risk of seizure recurrence in patients who had undergone epilepsy surgery.[21] This study did not demonstrate significant differences at 1 and 4 years in maintaining seizure-freedom between patients who had surgery, were seizure-free for at least a year, and tapered ASMs and those who had surgery, were seizure-free for at least 1 year and continued taking ASMs (31/34 [91%] vs 20/26 [77%], respectively; RR 1.185, 95% CI 0.937–1.499, $p>0.05$).

Conclusion

There is insufficient evidence to support or refute that the rate of seizure recurrence at 1 vs 4 years in patients who have undergone epilepsy surgery who discontinue ASMs is not significantly different from the rates in patients who continue taking ASMs (very low confidence, one Class III study).

Risk factors for seizure recurrence—Adults

Of the Class III studies, one study was in a mixed cohort of mostly adults.[13] In this study, the following factors were associated with a significantly increased odds of seizure recurrence: 2 years of seizure freedom at study entry, compared with longer times of seizure freedom (OR 2.6; 95% CI 1.5–4.8, $p<0.001$) and abnormal psychiatric examination results (OR 2.1; 95% CI 1.3–3.6, $p<0.004$). Duration of active disease, epilepsy syndrome, and abnormal CT/MRI results were not significant factors for an increased risk of seizure recurrence.

One Class III Medical Research Council (MRC) study looked at whether there was a difference among ASMs.[22] This study found that monotherapy with valproate, phenobarbitone and primidone, or phenytoin were associated with a significant risk of seizure recurrence following ASM withdrawal (HR 1.97, 95% CI 1.29–3.0, $p<0.004$; HR 3.55, 95% CI 1.24–10.2, $p<0.02$; and HR 3.02, 95% CI 1.84–4.97, $p<0.001$; respectively). This was not true for carbamazepine (HR 1.32, 95% CI 0.85–2.0). A second Class III MRC study created a risk index for seizure recurrence.[23] Using a Cox proportional hazards regression, they found 7 prognostic factors for increased risk of seizures: age of 16 years and older (RR 1.75, 95% CI 1.30–2.35), use of more than 1 ASM (RR 1.83, 95% CI 1.40–2.39), history of seizures after starting an ASM (RR 1.56, 95% CI 1.19–2.04), history of tonic-clonic seizures (RR 1.56, 95% CI 1.09–2.22), history of

myoclonic seizures (RR 1.84, 95% CI 1.13–3.01), and an abnormal EEG in the last year (RR 1.32, 95% CI 1.01–1.73).

Risk factors for seizure recurrence—Children

Three Class III prognostic studies in children were identified. One[18] found that an abnormal EEG before discontinuation was associated with seizure recurrence in children (RR 6.21, 95% CI 5.62–68.5, CI as given in paper). An abnormal EEG was defined as one with spikes, sharp waves, paroxysmal slowing, or non-paroxysmal abnormalities. Two Class III prognostic studies in the same cohort were identified.[24,25] The first[24] considered more than 20 factors; after Bonferroni correction, there were no statistically significant factors. The second[25] looked more specifically at EEG and found that among both groups of children (1-year and 3-year withdrawal), there was a higher risk of seizure recurrence in children with interictal epileptiform activity on the EEG (24 of 51 with epileptiform activity (47%) vs 31 of 94 without interictal epileptiform activity (33%), yielding an OR of 2.87 (95% CI 1.35–6.11, p=0.006).

Conclusions

Interictal epileptiform activity on EEG possibly increases the risk of seizure recurrence in children (low confidence, two Class III studies). Except for an epileptiform EEG, there is insufficient evidence to support or refute that a variety of risk factors predict a different chance of seizure recurrence (very low confidence, one Class I study in adults downgraded due to imprecision and generalizability). Neither of the included studies specified what kind of EEG was performed (e.g., length of study, sleep deprived); thus, we are unable to determine what length of EEG is needed to assess seizure recurrence risk.

For patients with epilepsy who take ASMs and who have been seizure-free for at least 12 months, does stopping ASMs, compared with not stopping, increase the risk of status epilepticus?

One Class I study addressed this question.[12] It did not find any significant predictors for the risk of status epilepticus (after Bonferroni correction); the study authors looked at age, gender, age of epilepsy onset, focal (partial) vs generalized epilepsy, MRI findings, duration of seizure freedom, specific ASMs, and a normal neurologic examination result.

No patients in the ASM withdrawal arm of the 1-year adult Class I randomized controlled trial had status epilepticus.[12] Most studies did not specifically mention any information about this.

Conclusion

ASM withdrawal possibly may not increase the risk of status epilepticus in adults. (low confidence, one Class I study, lowered due to imprecision).

For patients with epilepsy taking ASMs who have been seizure-free for at least 12 months, does stopping ASMs, compared to not stopping, reduce medication-related side effects?

There were no studies higher than Class IV that addressed this question.

For patients with epilepsy taking ASMs who have been seizure-free for at least 12 months, does stopping ASMs, compared to not stopping, change quality of life?

There was one Class I study that addressed this question.[12] It did not find significant differences in 3 quality of life measures, including the quality of life in epilepsy inventory-89 (mean score difference 0.3, 95% CI -1.55 to 2.07), between patients who withdrew ASMs and those who did not.

Conclusion

In adults who are seizure-free, ASM weaning possibly does not change quality of life (low confidence, one Class I study, downgraded due to data imprecision).

For patients with epilepsy taking ASMs who have been seizure-free for at least 12 months, does stopping ASMs, compared to not stopping, change the risk of mortality?

Only two studies specifically discussed mortality. During the 1-year adult Class I trial of ASM withdrawal, there were no deaths.[12] During the 6 years of follow-up of a Class III study,[14] two patients who continued ASMs died, most likely from a seizure.

Conclusion

There is insufficient evidence to support or refute that ASM withdrawal may change the risk of mortality in adults because there were no deaths in either arm of the trial (low confidence, one Class I and one Class III studies, downgraded due to imprecision).

For patients with epilepsy taking ASMs who have been seizure-free for at least 12 months, does stopping ASMs, compared with not stopping, change the risk of seizure recurrence based on the speed of medication withdrawal?

Two Class II studies addressed this question in children. In one Class II study, 57 patients tapered ASMs by 25% every 10 days or 25% every 2 months.[16] Kaplan-Meier survival curves over 54 months of follow-up were not significantly different between groups. In the other Class II study, ASMs were tapered at a rate of 25% every 2 weeks or 25% every 2 months.[17] No significant differences were present in the Kaplan-Meier survival curves across the 300 weeks of follow-up.

Conclusion

In children who are seizure free, withdrawal of ASMs at a rate of 25% every 10 days to 2 weeks is probably not significantly different in risk of seizure recurrence than withdrawal at a rate of 25% every 2 months throughout more than 4 years of follow-up (moderate confidence, 2 Class II trials).

PRACTICE RECOMMENDATIONS

Recommendations related to adults

Recommendation 1 rationale

There is low confidence that the risk of seizure recurrence is significantly higher among patients with a history of seizures who have been seizure free over 24–60 months who taper ASMs, when compared with patients who do not taper ASMs. Once epilepsy is masked, it is unknowable if you continue to have epilepsy or not. Patients should be part of the medical decision-making process, especially when there is clinical equipoise.

Although there is evidence for the predictive power of epileptiform abnormality in EEGs in children, there is no evidence above Class IV in adults. Moreover, the evidence in children cannot be used as related evidence in adults, as it is based on Class III data. The same applies for the small chance of medication resistance seen after ASM withdrawal.

To enable patients to make decisions, all the clinically relevant information should be made available. There are multiple factors in making this decision:

- Low-quality evidence suggests no difference in quality of life between patients with well-controlled epilepsy who stop versus continue taking ASMs.
- Factors contributing to quality of life are potentially highly individual and may include ease of ASM administration (e.g., dose frequency), experience of side effects, seizure recurrence, and comorbidities.
- In the 1-year follow-up of 1 trial, there were no deaths, and in the 6-year follow-up of the other trial the only deaths that occurred were in patients who continued taking ASMs. There does not seem to be an increased risk of status epilepticus in patients who are seizure-free for 2 years who withdrew ASMs; however, the risk of status epilepticus may be small in the cohorts of the study, and there may not be enough patients and time to detect a difference. There is no evidence that 2 years has special significance. It is well known that status epilepticus is cause of mortality in epilepsy patients.[26]

Recommendation statement 1a

In adults who are seizure-free for at least 2 years, there should be a discussion between the clinician and the patient and/or caregiver, if any, about the risks and benefits of ASM withdrawal, which specifically includes and documents:

1. there is possibly higher seizure recurrence in patients who had ASM withdrawal, and

2. that if seizures recur during or after withdrawal, there is a small chance they will no longer respond to medications (Level B).

Recommendation statement 1b

When discussing either ASM withdrawal or continuation with patients, since there is no statistically significant evidence to support either option, clinicians may consider individual patient characteristics and preferences (Level C).

Recommendation statement 1c

Counseling must include discussion that there is not strong evidence regarding the relationship between ASM withdrawal and changes in the risk of mortality and status epilepticus, and, as such, these risks have not been excluded by the evidence (Level A).

Recommendation statement 1d

Clinicians should counsel that recurrent seizures put people at risk for status epilepticus and death (Level B), although existing data do not suggest an increased risk of status epilepticus or death after ASM withdrawal.

Recommendation statement 1e

Clinicians must explore contributors to the quality of life of individual patients as part of shared decision-making regarding ASM discontinuation (Level A).

Recommendation statement 1f

Clinicians should discuss with seizure-free patients that it is unknown if EEG or imaging studies inform the decision to withdraw ASMs (Level B).

Recommendation 2 rationale

There is only 1 low-quality trial that examines the relationship between epilepsy surgery and ASM withdrawal, and no conclusions can be drawn from the trial.

Recommendation statement 2

Clinicians may discuss that the risk of seizure recurrence with ASM withdrawal in patients who have had epilepsy surgery and are seizure-free is uncertain due to the lack of evidence (Level C)

Recommendations related to children

Recommendation 3 rationale

There does not appear to be a statistically significant difference when ASMs are withdrawn in pediatric patients who have been seizure free for 2 years vs 4 years when patients have been seizure-free for 18–24 months during the first 4–6 years of follow-up. While the cohorts were broad, they do not include large numbers of children with electroclinical syndromes. When there is not significant difference between treatment and lack of treatment over long periods of time,

lack of treatment may be the preferred option. There is a small risk of becoming medication resistant with ASM withdrawal.

There is low confidence in evidence that an epileptiform EEG increases the risk of recurrence of seizure/s in children.

Patients and families of children who are seizure-free and contemplating ASM withdrawal would want any information about the withdrawal process that is available. The evidence suggests there is not a significant difference between weaning 25% every 10 days to 2 weeks vs 2 months.

Recommendation statement 3a

In children who are seizure-free for at least 18–24 months, who do not have an electroclinical syndrome suggesting otherwise, there should be a discussion about the risks and benefits of ASM withdrawal that specifically includes and documents that if seizures recur during either withdrawal or after withdrawal, there is a small chance they will no longer respond to medication (Level B).

Recommendation statement 3b

Clinicians should discuss with children and their families that ASM withdrawal can be considered because withdrawal of ASMs does not clearly increase risk of seizure recurrence (Level B).

Recommendation statement 3c

Clinicians should counsel that recurrent seizures put children at risk for status epilepticus and death (Level B), although existing data do not suggest an increased risk of status epilepticus or death after ASM withdrawal.

Recommendation statement 3d

Clinicians should explore contributors to quality of life for individual patients as part of shared decision-making regarding ASM withdrawal (Level B).

Recommendation statement 3e

In children seizure free for at least 18-24 months, if there is agreement between the physician, patient, and family to pursue consideration of ASM withdrawal, an EEG should be ordered (Level B).

Recommendation statement 3f

In children, seizure free for at least 18-24 months, in whom there is agreement between the physician, patient, and family to pursue consideration of ASM withdrawal, if the EEG does not show epileptiform activity, ASM withdrawal should be offered, at a rate no faster than 25% every 10–14 days (Level B).

Recommendation statement 3g

Clinicians must take into account the known natural history of the specific electroclinical syndrome when counseling about ASM withdrawal in children (Level A [no low to moderate risk of bias evidence]).

SUGGESTIONS FOR FUTURE RESEARCH

Future areas of study include the many gaps shown by this guideline. High-quality studies that answer the following questions and address the following statements are needed:

1. Is an EEG, or a modern MRI, or any genetic testing results a relevant prognostic factor in ASM withdrawal? Is there a specific kind of EEG, or other qualitative properties of the EEG, which are optimal?
2. Is there a certain speed of ASM withdrawal in adults that should be recommended?
3. Are there additional risks for people who experience recurrent seizures after ASM withdrawal? Should a different period of seizure-freedom be considered, or even considered at all, before a second ASM withdrawal is attempted?
4. Are there specific electroclinical syndromes (e.g., absence epilepsy, juvenile myoclonic epilepsy) that should or should not preclude consideration of ASM withdrawal?
5. More data is needed to address the rate of taper.
6. There is no current evidence to support the use of online seizure prediction tools. High-quality data is needed to demonstrate their validity.
7. Data about driving and ASM withdrawal and safety are needed.

Ideally a registry or consortia could be formed, which could have cohorts large enough to look at and examine if there are additional risks of status epilepticus or mortality or differences between adults and children.

CONFLICT OF INTEREST

The AAN is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. The AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2011 AAN process manual, as amended.[10]

DISCLAIMER

Clinical practice guidelines, practice advisories, comprehensive systematic reviews, focused systematic reviews, and other guidance published by the AAN and its affiliates are assessments of current scientific and clinical information provided as an educational service. The information (1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; (2) is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); (3) addresses only the question(s) specifically identified; (4) does not mandate any particular course of medical care; and (5) is not intended to substitute for the independent professional judgement of the treating provider, as the information does not account

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AUTHOR CONTRIBUTIONS

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		intellectual content, study supervision.
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Cynthia Harden, MD	Xenon Pharmaceuticals, Burnaby, Canada	Study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

REFERENCES

1. Murray CJL, Lopez AD. *Global comparative assessment in the health sector*. Geneva: World Health Organization; 1994.

2. GBD 2015 Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990–2015: a systemic analysis for the Global Burden of Disease Study 2015. Lancet Neurol 2017;16:877–897.

3. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. Epilepsia 1993;34:453–468.

4. Hauser WA, Beghi E. First seizure definitions and worldwide incidence and mortality. Epilepsia 2008;49:s8–s12.

5. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314–319.

6. Mohanraj R, Brodie MJ. Diagnosing refractory epilepsy: response to sequential treatment schedules. Eur J Neurol 2006;13:277–282.

7. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55:475–482.

8. American Academy of Neurology. A guideline for discontinuing antiepileptic drugs in seizure-free patients-Summary statement. Neurology 1996;47:600–602.

9. Sirven JI, Sperling MR, Wingerchuk DM. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. Cochrane Database Syst Rev 2001;(3): CD001902. DOI: 10.1002/14651858.CD001902.

10. American Academy of Neurology. *Clinical Practice Guideline Process Manual*. St. Paul: The American academy of Neurology; 2011.

11. Morris GL, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2013; 81: 1453–1439.

12. Lossius MI, Hessen E, Mowinckel P, Stavern K, Erikssen J, Gulbrandsen P, et al. Consequences of antiepileptic drug withdrawal: a randomized, double-blind study (Akershus Study). Epilepsia 2008;49:455–463.

13. Specchio LM, Tramacere L, La Neve A, Beghi E. Discontinuing antiepileptic drugs in patients who are seizure free on monotherapy. J Neurol Neurosurg Psychiatry 2002;72:22–25.

14. Randomised study of antiepileptic drug withdrawal in patients in remission. Medical Research Council Antiepileptic Drug Withdrawal Study Group. Lancet 1991;337:1175–1180.

15. Chadwick D, Taylor J, Johnson T. Outcomes after seizure recurrence in people with well-controlled epilepsy and the factors that influence it. Epilepsia 37:1043–1050.

16. Serra JG, Montenegro MA, Geurreiro MM. Antiepileptic drug withdrawal in childhood: does the duration of tapering off matter for seizure recurrence? J Child Neurol 2005;20:624–626.

17. Tennison M, Greenwood R, Lewis D, Thorn M. Discontinuing antiepileptic drugs in children with epilepsy: a comparison of a six-week and a nine-month taper period. N Engl J Med 1994;330 (20):1407–1410.

18. Gebremariam A, Mengesha W, Enqusilassie F. Discontinuing anti-epileptic medication(s) in epileptic children: 18 versus 24 months. Ann Trop Paediatr 1999;19:93–99.

19. Braathan G, Andersson T, Gylje H, et al. Comparison between one and three years of treatment in uncomplicated childhood epilepsy: a prospective study. I. Outcome in different seizure types. Epilepsia 1996;37:822–832.

20. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizure and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 2010;51:676–685.

21. Kerling F, Pauli E, Lorber B, Blumcke I, Buchfelder M, Stefan H. Drug withdrawal after successful epilepsy surgery: how safe is it? Epilepsy Behav 2009;15:476–480.

22. Chadwick D. Does withdrawal of different antiepileptic drugs have different effects on seizure recurrence? Further results from the MRC Antiepileptic Drug Withdrawal Study. Brain 1999;122:441–448.

23. Prognostic index for recurrence of seizures after remission of epilepsy. Medical Research Council Antiepileptic Drug Withdrawal Study Group. BMJ 1993;306:1374–1378.

24. Braathen G, Melander H. Early discontinuation of treatment in children with

uncomplicated epilepsy: a prospective study with a model for prediction of outcome. Epilepsia 1997;38:561–569.

25. Andersson T, Braathen G, Persson A, Theorell K. A Comparison between one and three years of treatment in uncomplicated childhood epilepsy: a prospective study. II. The EEG as predictor of outcome after withdrawal of treatment. Epilepsia 1997;38:225–232.

26. Ristić AJ, Sokić DV, Trajković G, Janković S, Vojvodić NM, Bascarević V, et al. Long-term survival in patients with status epilepticus: a tertiary referral center study. Epilepsia 2010;51:57–61.

APPENDICES

Appendix 1: AAN GS mission

The mission of the GS is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders. The GS is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix 2: AAN GS Members

Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-Chair), Sonja Potrebic, MD, PhD (Co-Vice-Chair), Stephen Ashwal, MD, Lori L. Billinghurst, MD, Brian Callaghan, MD, Gregory S. Day, MD, MSc, Diane Donley, MD, Richard M. Dubinsky, MD, MPH, Jeffrey Fletcher, MD, Gary S. Gronseth, MD (Senior Evidence-based Medicine Methodology Expert), Michael Haboubi, DO, John J. Halperin, MD, Yolanda Holler-Managan, MD, Annette M. Langer-Gould, MD, PhD, Nicole Licking, DO, Mia T. Minen, MD, Pushpa Narayanaswami, MBBS, DM, Maryam Oskoui, MD, Alejandro A. Rabinstein, MD, Alexander Rae-Grant, MD, Kevin Sheth, MD, Kelly Sullivan, PhD, Eric J. Ashman, MD (Ex-Officio), Jacqueline French, MD (Ex-Officio, Guideline Process Historian)

Appendix 3: Complete search strategy used in Medline, CENTRAL, DARE, and CINAHL

1. exp animals/ not humans.sh.
2. not 1
3. exp Epilepsy/

4. Seizures/

5. (epilep$ or seizure$ or convuls$).tw.

6. exp Anticonvulsants/

7. (anticonvulsant$ or antiepilep$).tw.

8. 3 or 4 or 5 or 6 or 7

9. (relapse or recurrence).ti,ab.

10. (remission and epilep$).ti,ab.

11. (discontinu$ or withdrawal).ti,ab.

12. (prognosis and epilep$).ti,ab.

13. 9 or 10 or 11 or 12

14. 2 and 8 and 13

Appendix 4: Evidence profile tables

Author	Class	Group Characteristics	Group size and comparator	Outcome measured	Results (including status and mortality if mentioned)
Lossius et al 2008	I	Adults with two or more unprovoked seizures, on monotherapy, Seizure-	79 with ASM withdrawal and placebo, 81 with continued ASMs, with a	Seizure relapse or 12 months had passed, Neuropsychiatric testing,	No serious harm during the 12 months of the study 5 of 77 (7%) non-withdrawers, 11

		freedom of 2 years, or >5 if prior withdrawal was attempted and failed. Exclusions: JME, paroxysmal activity with PGE, 2 prior withdrawal attempts, mental retardation, any comedication besides blood pressure, contraceptives, or thyroxine	discontinuation period of 12 weeks	HRQoL (Norwegian version) EEG Positive or negative risk factors for recurrence	of 72 (15%) withdrawers RR 2.46 (95% CI 0,85-7.08) Neuropsychiatric testing: no significant changes after Bonferoni correction, except for Lexical choice reaction time mean difference -24.42 (-34.11-8.74) (not sure what this means, since this is the wrong distribution[a]) HRQoL no significant difference EEG no change

					0 patients had status or mortality Risk factors for recurrence: CBZ ASM treatment (OR 2.86, 95% CI 1.31-6.26, p=0.01), normal neurological examination (OR 2.77, 95% CI 1.18-142.86, p=0.036)
Hessen et al 2006[b] (same cohort as Lossius et al 2008, but with some different information)	II	Adults with two or more unprovoked seizures, on monotherapy, Seizure-freedom of 2	This study reports on 75 with continued ASMs and 64 without continued ASMs. 150	The ten subtests of the CalCAP battery. Testing done 7 months after starting discontinuation.	After Bonferoni correction, the following subtests were statistically significant:

		years, or >5 if prior withdrawal was attempted and failed. Exclusions: JME, paroxysmal activity with PGE, 2 prior withdrawal attempts, mental retardation, any comedication besides ASA, contraceptives, or thyroxine	patients were randomized, leading to a completion rate of 93%	No explicit primary outcome, so downgraded to II.	Choice reaction time digits $p<0.01$ Discontinuation change -24.02 (56.07 SD) vs. Non-discontinuation 4.07 (33.29 SD) Language discrimination $p = 0.03$ Discontinuation change -17.44 (46.58 SD) vs Non-discontinuation 6.99 (45.79 SD) These differences were sustained when examining

					the subgroup on CBZ, but not VPA.
Hessen et al 2007[c] (part of the cohort reported in Lossius et al 2008)	II/III	Adults with two or more unprovoked seizures, on monotherapy, Seizure-freedom of 2 years, or >5 if prior withdrawal was attempted and failed. Exclusions: JME, paroxysmal activity with PGE, 2 prior withdrawal attempts, mental	Of the 150 randomized patients, 115 completed the MMPI (77%). Note there were differences in the baseline characteristics between the two groups in the entire group, but were balanced when looking at patients with therapeutic drug	MMPI (24 subscales) measured at baseline and at 7 months. No explicit primary outcome	After Bonferoni correction, there were no significant differences on any subscale. They looked at changes between (Class II) patients with therapeutic drug concentrations (Class III) patients with therapeutic drug concentrations taking CPZ

		retardation, any comedication besides ASA, contraceptives, or thyroxine	concentrations only.		
Serra et al 2005	II	Children with a diagnosis of epilepsy, and seizure control for at least 2 years. Patients with infantile spasms and neonatal seizures were excluded.	57 patients were split into two groups, randomized into dose reduction by 25% every 10 days and dose reduction by 25% every 2 months. No stated allocation concealment. No blinding.	Primary outcome was seizure recurrence over the 54 months of follow-up	There was no difference in Kaplan-Meier survival curve of the 10/30 patients in the 1-month group, and 12/27 patients in the 6-month group showed no significant differences.
Tennison et al 1994	II	Children with a diagnosis of	149 patients were split into	Primary outcome was	Testing was explored by

		epilepsy, who had been seizure-free for 18 months.	four groups, 133 completed (89%). Patients were split into 2 vs 4 years, and taper of 25% per 2 weeks vs 25% per 2 months	recurrence during the 300 weeks of follow-up	Kaplan-Meier survival curves. No significant difference seen in the rate of recurrence due to rate of medication tapering. No significant difference was seen in the rate of recurrence after 2 versus 4 years of seizure freedom.
Specchio et al 2002	III	A prospective dual cohort study, of patients with a diagnosis of epilepsy, who had been seizure free	No randomization. Patients/carers decided which cohort. There were baseline differences in the 330	Seizure relapse	The Hazard ratio for seizure relapse of patients with drug withdrawal was 2.9 (95% CI 1.8-4.6),

		for at least a year	enrolled patients.		The following factors were significant: 2 years of remission at study entry 2.6 (95% CI 1.5-4.8) Abnormal psychiatric examination 2.1 (95% CI 1.3-3.6)
Geabremariam et al 1999	III	A prospective, randomized open-label study, of children seizure-free for 18 months.	Coin flip by nurse unaware of study hypothesis. 41 tapered medication at 18 months, 39 at 24 months.	Seizure relapse.	They did not find significant difference in the risk of recurrence over the follow-up in this study, although mean follow-up was different for the two groups. The

					mean follow-up for immediate discontinuation was 38.3 months, and for waiting an additional six months was 23.9 months. During the period of follow-up, 12/41 (29%) who tapered at 18 months had recurrence, and 14/39 (36%) who tapered at 24 months had recurrence. Abnormal EEG at discontinuation was associated with seizure

					recurrence (RR 6.21, 95% CI 5.62-68.5). An abnormal EEG was defined as one with spikes, sharp waves, or paroxysmal slowing, and non-paroxysmal abnormalities.
Kerling et al 2009	III	A prospective cohort of patients who were completely seizure-free without any auras for 1 year after surgery	60 patients were stratified into two groups. No mention of randomization. 34 patients underwent 25% reduction every 3 months for each medication, 26	Primary outcome was seizure freedom.	2 years after surgery (1 year into study), 31/34 (91%) of the withdrawal group and 20/26 (77%) remained seizure-free (no significant difference). 5 years after surgery (4 years

			did not undergo reduction.		into study), 26/34 (76%) of the withdrawal group and 16/26 (62%) of the control group (no significant difference)
Braahan et al 1996	III	A prospective cohort of children aged 2-16, who were seizure-free for one year	207 children were randomized to medication withdrawal at 1 year to medication withdrawal at 3 years	Duration of remission after treatment withdrawal	77 (72%) in group I (one year seizure-freedom before medication withdrawal) and 84 (84%) children in group II (3-year period of seizure-freedom before medication withdrawal) were seizure-free during the last 6

					months of treatment. Relative risk for relapse 1.34 (95% CI 1.04-1.76, p=NS after Bonferroni correction).
Braathan et al 1997	III	Same cohort as Braathan 1996	Same cohort as Braathan 1996	23 predictive variables examined, no primary outcome	After Bonferroni correction, there were no significant differences for any of the variables looked at
Andersson et al 1997	III	Same cohort as Braathan 1996	Same cohort as Braathan 1996	Epileptiform activity	When all children were considered, the difference between epileptiform activity and no epileptiform

					activity was p=0.044, log-rank test. there was a higher risk of recurrence with epileptiform activity on EEG (24 of 51 with epileptiform activity (47%) versus 31 of 94 without epileptiform activity (33%), yielding an OR of 2.87 (95% CI 1.35 – 6.11, p=0.006).
MRC study 1991	III	Prospective, multicenter cohort study, seizure-free for at least 2	1021 patients were randomized to continued treatment,	Seizure recurrence	In the withdrawal group, there were 221 recurrences among the 510 patients that

		years, who were taking ASMs, and had 2 or more definitive seizures, included both adults and children	versus slow withdrawal of medication. Example withdrawal rate: phenytoin 50 mg per 4 weeks, children 1.5mg/kg/4 weeks.		group, whereas there were 133 recurrences among the 503 with continued therapy, yielding an odds ratio of 2.12 (95% CI 1.63 – 2.77, p<0.0001).
MRC 1993	III	Same cohort as MRC 1991	Same cohort as MRB 1991	Multivariate modelling	Age 16 and older (RR 1.75, 95% CI 1.30-2.35), >1 ASM (RR 1.83 95% CI 1.40 – 2.39), a history of seizures after starting an antiseizure medication (RR 1.56 95% CI 1.19 – 2.04), a history

					of tonic-clonic seizures (RR 1.56 95% CI 1.09 – 2.22), history of myoclonic seizures (RR 1.32 95% 1.01 – 1.73).
Chadwick et al 1996	III	Same cohort as MRC 1991	Same cohort as MRB 1991	Seizure recurrence	168 of the 221 recurrences in the withdrawal group, and 100 of the 133 recurrences in the medication continuation group having multiple recurrences. There was not a statistically significant difference in risk of multiple

					recurrences, if there was a single recurrence (OR 1.04 95% CI 0.63 – 1.72, p<0.86). They concluded that although the risk of seizures increases in the first 1-2 years, there is no evidence for a difference in long-term outcome.
Chadwick et al 1999	III	Same cohort as MRC	Same cohort as MRC	Seizure recurrence	monotherapy with valproate (hazard ratio 1.97 95% CI 1.29 – 3.0), phenobarbitone and primidone (hazard ratio 3.55

					95% CI 1.24 – 10.2), and phenytoin(hazard ratio 3.02 95% CI 1.84 0 4.97), there was significant risk for seizure recurrence with medication withdrawal, while for carbamazepine, this was not true (hazard ratio 1.32 95% CI 0.85 – 2.0).

[a]Hauk O, Coutout C, Holden A, Chen Y. The time-course of single-word reading: evidence from fast behavioral and brain responses. Neuroimage 2012;60:1462–1477.

[b]Hessen E, Lossius MI, Reinvang I, Gjerstad L. Influence of major antiepileptic drugs on attention, reaction time, and speed of information processing: results from a randomized, double-

blind, placebo-controlled withdrawal study of seizure-free epilepsy patients receiving monotherapy. Epilepsia 2006;47: 2038–2045.

[c]Hessen E, Lossius MI, Reinvang I, Gjerstad L. Slight improvement in mood and irritability after antiepileptic drug withdrawal: a controlled study in patients on monotherapy. Epilepsy Behav 2007;10:449–455.

Appendix 5: Evidence synthesis tables (Available upon request)

Appendix 6: Rationale of factors considered in developing the practice recommendations

In this appendix, *EVID* refers to evidence systematically reviewed; *RELA* to strong evidence derived from related conditions; *PRIN* to axiomatic principles of care; and *INFER* to inferences made from one or more statements in the recommendation rationale.

In the tables that follow, consensus is considered to have been reached if 80% or more of the guideline panel agree on the strength of a given domain. For nonpremise domains, intensity of shading corresponds to the number of panel members who were in agreement (shading of greater intensity indicates a larger number of panel members who reached agreement). The strength of the recommendation is anchored to the strength of the inference. The recommendation strength can be downgraded for any modifier; it can be upgraded only by one level for a moderate to large benefit relative to harm. In addition, domains include the premises and factors on which the recommendations are based.

PRACTICE RECOMMENDATIONS

Recommendations related to adults

Recommendation 1 rationale

There is low confidence that the risk of seizure recurrence is significantly higher among patients with a history of seizures who have been seizure free over 24–60 months who taper ASMs, when compared to patients who do not taper ASMs (EVID). Once epilepsy is masked, it is unknowable if you continue to have epilepsy or not (PRIN). Patients should be part of the medical decision-making process, especially when there is clinical equipoise (PRIN).

Although there is evidence for the predictive power of epileptiform abnormality in EEGs in children (EVID), there is no evidence above Class IV in adults. Moreover, the evidence in children cannot be used as related evidence in adults, as it is based on Class III data. The same applies for the small chance of medication resistance seen after ASM withdrawal. These differences may relate to biological differences between children and adults as well as the differences in epilepsy between adults and children (PRIN).

To enable patients to make decisions, all the clinically relevant information should be made available (PRIN). There are multiple factors in making this decision:

- Low-quality evidence suggests no difference in quality of life between patients with well-controlled epilepsy who stop versus continue taking ASMs (EVID).

- Factors contributing to quality of life are potentially highly individual and may include ease of ASM administration (e.g., dose frequency), experience of side effects, seizure recurrence, and comorbidities (PRIN).
- In the 1-year follow-up of 1 trial, there were no deaths, and in the 6-year follow-up of the other trial the only deaths that occurred were in patients who continued taking ASMs (EVID). There does not seem to be an increased risk of status epilepticus in patients who are seizure-free for 2 years who withdrew ASMs; however, the risk of status epilepticus may be small in the cohorts of the study, and there may not be enough patients and time to detect a difference (EVID). There is no evidence that 2 years has special significance (EVID). It is well known that status epilepticus is cause of mortality in epilepsy patients (RELA).[26]

Recommendation statement 1a

In adults who are seizure-free for at least 2 years, there should be a discussion between the clinician and the patient and/or caregiver, if any, about the risks and benefits of ASM withdrawal, which specifically includes and documents:

1. there is possibly higher seizure recurrence in patients who had ASM withdrawal, and

2. that if seizures recur during or after withdrawal, there is a small chance they will no longer respond to medications (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 3	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 2	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 3	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation statement 1b

When discussing either ASM withdrawal or continuation with patients, since there is no statistically significant evidence to support either option, clinicians may consider individual patient characteristics and preferences (Level C).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	NA
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 2	Very important 2	Critically important 1	Yes
Variation in preferences	Large 0	Moderate 1	Modest 2	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 0	Usually 0	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 0	Small 5	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation statement 1c

Counseling must include discussion that there is not strong evidence regarding the relationship between ASM withdrawal and changes in the risk of mortality and status epilepticus, and, as such, these risks have not been excluded by the evidence (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	NA
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 2	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 0	Modest 1	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation statement 1d

Clinicians should counsel that recurrent seizures put people at risk for status epilepticus and death (Level B), although existing data do not suggest an increased risk of status epilepticus or death after ASM withdrawal.

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 3	Yes
Importance of outcomes	Not important or unknown 1	Mildly Important 0	Very important 1	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 0	Modest 1	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation statement 1e

Clinicians must explore contributors to the quality of life of individual patients as part of shared decision-making regarding ASM discontinuation (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	NA
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 2	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 0	Modest 2	Minimal 3	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 3	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation statement 1f

Clinicians should discuss with seizure-free patients that it is unknown if EEG or imaging studies inform the decision to withdraw ASMs (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 3	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 1	Yes
Variation in preferences	Large 0	Moderate 1	Modest 2	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 3	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 3	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 2 rationale

There is only one low-quality trial that examines the relationship between epilepsy surgery and ASM withdrawal, and no conclusions can be drawn from the trial (EVID).

Recommendation statement 2

Clinicians may discuss that the risk of seizure recurrence with ASM withdrawal in patients who have had epilepsy surgery and are seizure-free is uncertain due to the lack of evidence (Level C)

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	NA
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	NA
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	NA
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 0	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 2	Very important 2	Critically important 1	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 3	Yes
Strength of recommendation	R/U	C	B	A	

Recommendations related to children

Recommendation 3 rationale

There does not appear to be a statistically significant difference when ASMs are withdrawn in pediatric patients who have been seizure free for 2 years vs 4 years when patients have been seizure-free for 18–24 months during the first 4–6 years of follow-up (EVID). While the cohorts were broad, they do not include large numbers of children with electroclinical syndromes. When there is not significant difference between treatment and lack of treatment over long periods of

time, lack of treatment may be the preferred option (PRIN). There is a small risk of becoming medication resistant with ASM withdrawal (PRIN).

There is low confidence in evidence that an epileptiform EEG increases the risk of recurrence of seizure/s in children (EVID).

Patients and families of children who are seizure-free and contemplating ASM withdrawal would want any information about the withdrawal process that is available (PRIN). The evidence suggests there is not a significant difference between weaning 25% every 10 days to 2 weeks vs 2 months (EVID).

Recommendation statement 3a

In children who are seizure-free for at least 18–24 months, who do not have an electroclinical syndrome suggesting otherwise, there should be a discussion about the risks and benefits of ASM withdrawal that specifically includes and documents that if seizures recur during either withdrawal or after withdrawal, there is a small chance they will no longer respond to medication (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	NA
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	NA
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 2	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation statement 3b

Clinicians may discuss with children and their families that ASM withdrawal can be considered because withdrawal of ASMs does not clearly increase risk of seizure recurrence (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 1	Benefit >>> harm 3	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 1	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation statement 3c

Clinicians should counsel that recurrent seizures put children at risk for status epilepticus and death (Level B), although existing data do not suggest an increased risk of status epilepticus or death after ASM withdrawal.

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	NA
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	NA
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 0	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 0	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 0	Modest 2	Minimal 3	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 0	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation statement 3d

Clinicians should explore contributors to quality of life for individual patients as part of shared decision-making regarding ASM withdrawal (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 2	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation statement 3e

In children seizure free for at least 18-24 months, if there is agreement between the physician, patient, and family to pursue consideration of ASM withdrawal, an EEG should be ordered (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	NA
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	NA
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 3	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 1	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 2	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 5	Small 0	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation statement 3f

In children, seizure free for at least 18-24 months, in whom there is agreement between the physician, patient, and family to pursue consideration of ASM withdrawal, if the EEG does not show epileptiform activity, ASM withdrawal should be offered, at a rate no faster than 25% every 10–14 days (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	NA
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	NA
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 3	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 2	Yes
Variation in preferences	Large 0	Moderate 1	Modest 3	Minimal 1	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 1	Small 3	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation statement 3g

Clinicians must take into account the known natural history of the specific electroclinical syndrome when counseling about ASM withdrawal in children (Level A [no low to moderate risk of bias evidence]).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 0	Benefit >>> harm 5	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 1	Critically important 4	Yes
Variation in preferences	Large 0	Moderate 0	Modest 2	Minimal 3	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 0	Small 4	Yes
Strength of recommendation	R/U	C	B	A	